AD_____

Award Number: DAMD17-03-1-0708

TITLE: A Randomized Study of the Effects of Tibolone on Bone Density, Menopausal Symptoms, and Breast Density in High-Risk Women After Prophylactic Oophorectomy

PRINCIPAL INVESTIGATOR: Judy Garber, Principal Investigator
Meryl LeBoff, MD, Co-investigator
Hadine Joffe, MD, Co-investigator
Nancy Lin, MD, Co-investigator
Paula Ryan, MD, Co-investigator

CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute
Boston MA 02115

REPORT DATE: September 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-09-2005	Annual	01 Sep 03 – 31 Aug 05

4. TITLE AND SUBTITLE
A Randomized Study of the Effects of Tibolone on Bone Density, Menopausal Symptoms, and Breast Density in High-Risk Women After Prophylactic Oophorectomy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-03-1-0708

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Judy Garber, Principal Investigator; Meryl LeBoff, MD, Co-investigator; Hadine Joffe, MD, Co-investigato; Nancy Lin, MD, Co-investigator; Paula Ryan, MD, Co-investigator
E-Mail: judy_garber@dfci.harvard.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Dana-Farber Cancer Institute
Boston MA 02115

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The synthetic steroid tibolone has been shown to improve bone mass, mitigate menopausal symptoms and reduce breast density in women with natural menopause. It has not been evaluated in an abrupt menopause model, as occurs in women at high risk of breast cancer because of inherited risk who undergo prophylactic oophorectomy to reduce breast cancer risk. We will conduct a double-blind randomized placebo-control trial to test the hypotheses that Tibolone will accomplish these goals in high-risk premenopausal women undergoing prophylactic oophorectomy, and provide an alternative for them to manage menopause symptoms without increasing breast cancer risk. Our progress to date (report 9/1/04 – 8/31/05) has been: 1. Resubmission of revised protocol to DFCI IRB in August, 2004 2. ORP review of protocol at meeting 03/05 were communicated to PI and required extensive revision of the protocol to eliminate the additional medications added for menopause symptom management that had not been included as part of the original proposal and were felt to affect the potential integrity of the study. 3. Preparations for resubmission of the protocol to DOD and FDA

15. SUBJECT TERMS
clinical trial; genetic risk; hormone activity; chemoprevention

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	6	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

Introduction

Women with germline *BRCA1* and *BRCA2* mutations face a lifetime risk of breast cancer of 36-87%, as well as high risks of ovarian cancers, approximately 40% and 20%, respectively. Women who test positive for deleterious *BRCA1/2* mutations are advised to undergo frequent cancer screening and to consider prophylactic surgery. In particular, prophylactic bilateral salpingo-oophorectomy is recommended for premenopausal women because of strong data demonstrating not only a reduction in ovarian cancer risk exceeding 90% in the face of ineffective early detection strategies, but also reduction in breast cancer risk of approximately 50%. However, the optimal timing of surgery is debated, since oophorectomy induces premature menopause, with all of the implications of early estrogen deficiency, including an increased risk of osteoporosis and vasomotor symptoms. Hormone replacement therapy has been shown to increase breast cancer risk in the general population, creating a difficult dilemma for young mutation carriers who undergo surgery to improve survival, but often at a significant cost in quality of life. In this project, we propose to evaluate the agent Tibolone, a synthetic steroid with an attractive safety and efficacy profile, for its ability to prevent bone loss, mitigate menopause symptoms, and modulate breast density in high risk women following prophylactic oophorectomy. We hope to provide these women with a safe and effective alternative for management of menopause symptoms and consequences after risk-reducing prophylactic surgery.

Body

Task 1. Finalize protocol :

a. Protocol had been revised with input from the research team at Dana Farber and associated institutions. Recommendations were made to add SSRI agents for effective management of menopause symptoms in order to keep subjects in the protocol who did not experience relief of symptoms on the placebo arm. The protocol was submitted to the Harvard IRB as well as the DOD ORP. The ORP provided extensive review, and required that the protocol be revised to simplify menopause symptom management in order to ensure that the primary endpoints could still be addressed in the analysis. Resubmission to all necessary regulatory bodies as per instructions from the DOD ORP is in progress. Resubmission to the FDA is also going to be necessary(IND 73,953), target date 10/05. .
b. Protocol data collection and patient education instruments are also undergoing revision for centralized data management. Study nurses and managers have been alerted that the protocol would have a more restricted symptom management scheme.
c. Finalize protocol implementation at two cooperating institutions. The protocol has been approved for the institutions; the labs prepared; the study staff trained; the data collection systems established, and recruitment strategies ready to begin as soon as DAMD human subjects review and investigator response to the review (revision as indicated) are complete.

Task 2. Recruitment of study participants (Year 2)

a. Enroll women with BRCA1/2 mutations from two clinical cancer genetics clinics who are unaffected with cancer, are premenopausal, and who plan prophylactic mastectomy within 2 months of signing consent to participate. Participating sites continue to identify new women with germline mutations who are undergoing prophylactic oophorectomy who will comprise the potential study population for this trial. The gynecologic oncology surgeons have been made aware of the trial and are prepared to refer women to the study. Systems for consenting and enrolling perspective participants have not been modified.

Task 3. Obtain study measurements at specified intervals: baseline, 6 months and 12 months.
No work has been done on this task

a. Obtain bone mineral density and markers of bone turnover at baseline (end of hormone replacement), 6 months and 12 months on medication
b. Obtain baseline and 12 month mammograms from all sites. Batched mammograms will be collected for digitization and breast density calculation
c. Collect baseline menopause symptom data using standardized instruments
d. After 2 months without adjuvant medications, add agents intended to mitigate menopause symptoms in specified manner, measuring menopause symptoms on these additional agents.

Task 4. Data analysis, manuscript preparation
No work has been done on this task

a. Data for the three specific aims will be entered, cleaned and analysed
b. Manuscripts will be prepared addressing the 3 specific effects of tibolone compared to placebo: bone, menopause symptoms and mammographic breast density.
c. The final report will be prepared.

Key Research Accomplishments

- We have developed and and obtained institutional IRB approval of the research protocol, recruitment and study management materials;
- We have developed and piloted algorithms for symptom management, trained research nurses to use them for management of patients with menopause symptoms and breast cancer or breast cancer risk;
- We have obtained Tibolone and placebo. The protocol is ready for initiation after DAMD Human Subjects approval.
- We have developed systems for patient accrual working with gynecologic oncologists in involved institutions.
- We are revising the protocol in accordance with requirements from the DOD-ORP.

Reportable Outcomes Not applicable

Conclusion To date, we have developed the protocolfor conduct of th for conduct of the study, as well as all pertinent recruitment and data collection materials, and have trained the study nurses. We are looking forward to proceeding with implementation of the protocol as soon as we revise our materials in accordance with DAMD suggestions and required changes so can begin the trial.

References Not Applicable

Appendices Not Applicable